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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/041,054	01/07/2002	Andrew Darrow	ORT-1560	3780

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EXAMINER

MOORE, WILLIAM W

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 07/10/2003

5

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/041,054	DARROW ET AL.	
	Examiner	Art Unit	
	William W. Moore	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-9, 14 and 21 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-9, 14 and 21 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☒ Claim(s) 3, 6, and 9 are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>3</u> . | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Response to Amendment

Applicant's Amendment A, Paper No. 2 filed January 7, 2002, has been entered, canceling claims 10-13, 15-20 and 22-27 and providing a reference at line 1, page 1, of the specification to the parent application serial No. 09/386,653, which has issued on October 1, 2002, as U.S. Patent No. 6,458,564, made of record herewith.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claims 1, 4, and 9, drawn in part, and claims 2, 3, 5, 8, 14, and 21 drawn entirely, to a nucleic acid molecule comprising a region of a mRNA transcript encoding a human serine protease T, a region of a corresponding cDNA copy encoding a human serine protease T, or variant thereof, to expression vectors comprising the nucleic acid molecule encoding a human serine protease T, to host cells comprising the nucleic acid molecule, to recombinant methods of making the encoded protease using the vectors and host cells, and to a kit comprising said nucleic acid molecule, classified, *inter alia*, in class 435, subclass 69.1.

II. Claims 3, 6 and 9, drawn in part to an expression vector comprising a genomic DNA molecule encoding a human serine protease T and to host cells comprising the nucleic acid sequence, classified in class 536, subclass 23.2

Inventions of Group II and Group I are related as combination and subcombination. Inventions in this relationship are distinct if it can be shown that (1) the combination as claimed does not require the particulars of the subcombination as claimed for patentability, and (2) that the subcombination has utility by itself or in other combinations (MPEP § 806.05(c)). In the instant case, the combination as claimed does not require the particulars of the subcombination as claimed because the combination provides further DNA sequence elements, such as external and internal regulatory sequence elements and internal introns, that provide further diagnostic and production applications. The subcombination, which includes an embodiment with a heterologous coding region, has separate utility such as expression of an active fusion product suitable for rapid isolation.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

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During a telephone conversation with Ms. Myra McCormack on August 15, 2002, a provisional election was made **with** traverse to prosecute the invention of Group I, claims 1-9, 14 and 21. Affirmation of this election must be made by applicant in replying to this Office action. Claims 1-9, 14 and 21 are examined to the extent they describe a nucleic acid which is a cDNA, a mRNA, or a synthetic DNA encoding a protease T protein, and the subject matter of genomic DNA sequences of claims 3, 6, and 9 encoding a protease T protein are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claim Rejections - 35 USC §112

The following is a quotation of the first paragraph of 35 U.S.C. §112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 and 14 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claim 21 is not subject to this rejection because it requires that a claimed kit comprise one of the several nucleic acid sequences that the specification specifically defines. The specification fails to provide an adequate written description of a nucleic acid that encodes any "functional derivative" of the native protease T amino acid sequence set forth in SEQ ID NO:7 other than a nucleic acid that encodes the zymogen fusion having the amino acid sequence set forth in SEQ ID NO:9. There is no evidence in the specification that Applicant possessed a derivative, or a fragmentary, nucleotide sequence of SEQ ID NO:2, a subject matter included in claims 1, 3, 7 and 21, that could encode a functional catalytic domain protease with an amino acid sequence differing from the amino acid sequence of SEQ ID NO:7 at the time the parent application was filed. With regard to subject matter described by claim 2, Applicant indeed possessed a fragment of the nucleic acid sequence

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of SEQ ID NO:1, a fragment encoding the catalytic domain region of SEQ ID NO:7 which is part of the nucleic acid sequence of SEQ ID NO:8 that specifies the fusion construct of SEQ ID NO:9. The protease having the amino acid sequence of SEQ ID NO:9 is an artificial product, a fusion polypeptide of heterologous domains, thus is not disclosed to be fragmentary in any respect and must possess the amino acid sequence of the protease T catalytic domain to provide catalytic activity.

It is agreed that SEQ ID NO:8 is a derivative species of SEQ ID NO:1 wherein Applicant fused a region encoding the native protease T catalytic domain to heterologous nucleic acid sequences. While Applicant and others can replace, e.g., the native signal peptide of a human T protease, with a different signal peptide region just as Applicant introduced an alternative signal peptide, a polyhistidine tag, and an alternative propeptide region in preparing a baculovirus vector expression construct, nothing in the specification shows that Applicant had determined, or even contemplated, those positions among the carboxyl-proximal 260 amino acids of the T protease that might be altered, nor the nature of any amino acid substitution, nor any deletion of amino acids to generate a fragment. Thus the specification provides no written description supporting subject matter described primarily in functional terms in claims 1-9 and 14.

Claims 1-9 and 14 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for nucleic acid molecules encoding a serine protease T having the catalytic domain amino acid sequence set forth in SEQ ID NO:7, and vectors, transformed host cells, kits, and methods of recombinant production of a protease comprising, or utilizing, said nucleic acid molecules,

does not reasonably provide enablement for nucleic molecules encoding any and all alternative, "functional derivatives", of the serine protease T having amino acid sequences that diverge from the catalytic domain of the protease comprised by SEQ ID NO:7. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 21 is not subject to this rejection because it requires that a claimed kit comprise one of the several nucleic acid sequences specifically enabled by the specification. It is agreed that isocoding DNA encoding the catalytic domain present both in the native

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protease T having the amino acid sequence set forth in SEQ ID NO:7 and the zymogen-protease T fusion protein having the amino acid sequence set forth in SEQ NO:9 are enabled by the state of the art taken together with the specification. Claims 1-9 and 14, however, embrace, in reciting "functional derivatives" and "protease T protein", arbitrary assignments of any or all codon deletions, additions, or substitutions in nucleic acid sequences encoding the amino acid sequence of the human protease T catalytic domain of SEQ ID NO:7, as well as resulting, divergent, catalytic domains with unspecified numbers of amino acid substitutions, additions or deletions. The specification does not teach one of skill in the art where, or how, nucleic acid sequences encoding the T protease catalytic domain within SEQ ID NO:7 might be altered by introducing any number of alternative codons and still permit expression of a functioning catalytic domain comprising unspecified amino acid insertions, deletions, or substitutions anywhere, in any combination or pattern.

It is well settled that 35 U.S.C. §112, first paragraph, requires that a disclosure be sufficiently enabling to allow one of skill in the art to practice the invention as claimed without undue experimentation and that unpredictability in an attempt to practice a claimed invention is a significant factor supporting a rejection under 35 U.S.C. §112, first paragraph, for non-enablement. See, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (recognizing and applying the "Forman" factors). Cf., *Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986) (citing eight factors relevant to analysis of enablement). The standard set by the CCPA, the predecessor of the Court of Appeals for the Federal Circuit, is not to "make and screen" any and all possible alterations because a reasonable correlation must exist between the scope of guidance provided by the specification and the scope asserted in the claimed subject matter. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 25 (CCPA 1970) (scope of enablement varies inversely with the degree of unpredictability of factors involved in physiological activity of small peptide

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hormone); see also, *Ex parte Maizel*, 27 USPQ2d 1662, 1665 (Bd. Pat. App. & Int. 1992) (functional equivalency of divergent gene products not supported by disclosure only of a single B-cell growth factor allele). The standard set by the CCPA was approved by the Federal Circuit in *Genentech, Inc. v. Novo-Nordisk A/S*, 42 USPQ2d 1001 (Fed. Cir. 1997). In considering whether definitional statements might enable a claim scope that extended beyond a disclosed, recombinantly-produced, gene product having a native amino acid sequence to embrace a specific variant gene product encoded by an altered DNA sequence, the Federal Circuit held that only a narrow structural and functional definition was enabling because sweeping definitions of scope in the patent specification could not reasonably have been relied upon by the PTO in issuing the patent. *Genentech, Inc. v. The Wellcome Found. Ltd.*, 29 F.3d 1555, 1564-65, 31 USPQ2d 1161, 1168 (Fed. Cir. 1994). Applying the "Forman" factors discussed in *Wands*, to the scope of the claims rejected, it is apparent that:

- a) the specification lacks adequate, specific, guidance for altering DNA sequences coding for, and encoded amino acid sequences of, the catalytic domain of the T protease comprised by SEQ ID NO:7,
- b) the specification lacks working examples wherein the amino acid sequence of the T protease catalytic domain comprised by SEQ ID NO:7 is altered,
- c) in view of the prior art publications of record herein, the state of the art and level of skill in the art do not support such alteration, and,
- d) unpredictability exists in the art where no catalytic domains of related S1 proteases have sustained alterations beyond that disclosed in the fusion protein having the amino acid of SEQ ID NO:7 yet retained their proteolytic activity.

The scope of subject matters of nucleic acid sequences encoding proteins having amino acid sequences differing from the protease T catalytic domain amino acid sequence within SEQ ID NO:7 embraced by the phrases, "functional derivatives" and "protease T protein" is not supported by the specification, even if taken in combination with the teachings available in the art. Amending claims 1, 2, 4, 5, 8, and 14 to limit their subject matters as indicated in the statement at page 4 above will overcome this rejection.

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The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4-9, 14 and 21 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4, 5, 14, and 21 are indefinite in reciting "protease T protein" because, while the specification discloses that the human protease T is a protease, i.e., that it cleaves peptide bonds, the phrase is ambiguous where it is open to an interpretation that some other form of function, a "protein" function not disclosed in the specification, is intended. Claims 6-9 are subject to this rejection because they incorporate the indefinite limitations of claims 4 and 5 from which they depend without resolving the ambiguity.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-9 are rejected under 35 U.S.C. § 102(b) as being anticipated by Antalis et al., WO 98/36054, submitted with Applicant's Information Disclosure Statement.

Antalis et al. disclose, see Figure 20C, SEQ ID NO:30, pages 10, 18, and Example 15 at pages 52-53 and claims 19-21, 26, and 27, a nucleotide sequence encoding a serine protease designated SPO03LA having a deduced amino acid sequence sharing 100% sequence identity with the amino acid sequence of the native T protease from position 26 to position 290, inclusive. The catalytic domain of the SPO03LA product that Antalis et al. identify as a serine protease is entirely identical to the catalytic domain of the native protease T disclosed herein, lacking only a portion of the signal peptide region to share complete identity with the protease T amino acid sequence of SEQ ID NO:7 of the instant application and sharing the same activation site sequence, thus the cDNA of SEQ ID NO:30 of Antalis et al. clearly anticipates a nucleic acid molecule encoding a "functional

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derivative" of a protease T having the amino acid sequence set forth in SEQ ID NO:7 of claims 1-3 herein. Antalis et al. further disclose, pages 38 and 39, expression vectors and host cells comprising a nucleotide sequence encoding a SP003LA serine protease in a context for expression by the host cell, which may be a prokaryotic or an eukaryotic host cell, anticipating the subject matters of claims 4-9 herein because they need not disclose construction of a particular expression vector comprising a SP003LA-encoding nucleotide sequence, or transformation of a particular host cell with such an expression vector, to meet generic limitations of claims 4-9 herein where a great variety of such vectors and host cells were well-known and commonly-used in the art at the time the invention was made.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. §103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. §103(c) and potential 35 U.S.C. §§102(e), (f) or (g) prior art under 35 U.S.C. §103(a).

Claims 14 and 21 are rejected under 35 U.S.C. §103(a) as obvious over Antalis et al., WO 98/36054, as applied to claims 1-9 above, in view of Burgess et al., U.S. Patent No. 6,165,771, also submitted with Applicant's Information Disclosure Statement.

The disclosures of Antalis et al. of a nucleotide sequence encoding a serine protease designated SP003LA having a deduced amino acid sequence sharing 100% sequence identity with the amino acid sequence of the native T protease from position 26 to position 290, inclusive, and of expression vectors and host cells comprising a SP003LA-

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encoding nucleotide sequence, discussed above, are taken as before. Antalis et al. do not disclose a process for expression of the SP003LA serine protease in recombinant host cells, nor disclose the preparation of a kit comprising a nucleic acid sequence encoding a SP003LA, which inherently constitutes a very large fragment of a nucleic acid sequence encoding the protease T of SEQ ID NO:7 of the instant application. Thus the further teaching of Antalis et al., page 53, is now cited: That the SP003LA-encoding nucleic acid sequence is present in a human chromosomal cluster of serine protease genes comprising the human testisin gene, established by Antalis et al. to contribute to spermatogenesis and also to be implicated in testicular cancer, and that these serine proteases genes may be "essential" for the processes of "sperm maturation and development", where the "loss or mutation of these genes may lead to testicular germ cell tumours and to other testicular abnormalities, such as infertility."


Burgess et al., available as prior art under 35 U.S.C. §102(e) to an invention claimed herein in view of its earlier priority date, teach the recombinant expression of the medically significant human serine protease designated HE2NW40, cols. 5-9, in several prokaryotic and eukaryotic host cell transformed with an expression vector comprising a polynucleotide encoding the HE2NW40 product, or variants thereof such as fusion polypeptides made suitable for extracellular secretion by a selected host cell or made suitable for recovery by affinity chromatography from the host cell culture or from lysed host cells after expression, in order to prepare diagnostic antisera to detect the presence or absence of the expression of the native human serine protease HE2NW40 in cells of human tissues. Burgess et al. also teach, col. 8, the preparation of a diagnostic kit comprising a polynucleotide encoding the human serine protease HE2NW40, or a fragment thereof, useful in diagnosing a disease or susceptibility to a disease. It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the SP003LA-encoding nucleotide

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sequence of Antalis et al. for the HE2NW40-encoding nucleotide sequence in a vector and host cell of the recombinant expression system of Burgess et al. in order to practice a method for expression of the SP003LA serine protease in recombinant host cells according to claim 14 herein and would also have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the SP003LA-encoding nucleotide sequence of Antalis et al., or a fragment thereof, for the HE2NW40-encoding nucleotide sequence, or a fragment thereof, in a diagnostic kit of Burgess et al. to prepare kit of claim 21 herein. This is because both Antalis et al. and Burgess et al. teach that their respective SP003LA-encoding and HE2NW40-encoding nucleotide sequences encode proteases that are associated with human disease states, or with susceptibility to disease in humans, and because Burgess et al. teach that it is advantageous to recombinantly express a human serine protease encoded by a human serine protease-encoding polynucleotide in order to recover the expressed protease and to prepare diagnostic antisera therewith, and because Burgess et al. also teach that it is advantageous to prepare a diagnostic kit comprising a human serine protease-encoding polynucleotide, or a fragment thereof, in order to use the kin in the diagnosis of a disease or a susceptibility to a disease.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 703.308.0583. The examiner can normally be reached between 9:00AM-5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached at 703.308.3804. Further fax phone numbers for the organization where this application or proceeding is assigned are 703.308.4242 for regular communications and 703.308.0294 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703.308.0196.


William W. Moore
July 3, 2003